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Introduction: High-dose, post-transplantation cyclophosphamide (PTCy) is effective as single-agent graft-versus-host disease (GVHD) prophylaxis after myeloablative conditioning (MAC) and human leukocyte antigen (HLA)-matched-related or -unrelated allogeneic bone marrow transplantation (alloBMT), producing grade III-IV acute GVHD and chronic GVHD rates of approximately 10-15% each. However, it is unknown whether plasma-derived proteomic biomarkers previously established using other transplantation platforms are applicable to PTCy-treated patients.

Methods: Plasma was obtained from the peripheral blood of 100 adult patients, 70 of whom received busulfan/fludarabine MAC and 30 of whom received busulfan/cyclophosphamide MAC, at month 1 and month 2-3 post-transplant. Twelve healthy controls were used as a comparative group. Plasma was analyzed using ELISA for interleukin-2 receptor alpha (IL-2rα), IL-6, tumor necrosis factor receptor-1 (TNFR-1), elafin, regenerating islet-derived 3-alpha (REG3α), suppression of tumorigenicity 2 (ST2), and chemokine (C-X-C motif) ligand 9 (CXCL9).

Results: Plasma levels of 6 of the 7 putative biomarkers were significantly elevated ($p<0.0001$) in patients at 1 month post-transplant compared with healthy controls; only elafin levels were similar between patients and controls. Plasma levels of IL-2rα ($p=0.038$), CXCL9 ($p=0.0003$), and IL-6 ($p=0.032$) at 1 month post-transplant were elevated in patients who would subsequently develop grade II-IV acute GVHD. There also was a tendency of a relationship ($p=0.06$) between elevated elafin levels at 1 month post-transplant and grade II-IV acute GVHD development. None of the 7 biomarkers at post-transplant month 1 was prognostic of chronic GVHD development. However, elevated REG3α levels at month 2-3 were prognostic of the subsequent development of chronic GVHD ($p=0.027$). Elevations in 4 of the 7 biomarkers (IL-2rα, $p=0.014$; IL-6, $p=0.024$; TNFR-1, $p=0.033$; and ST-2, $p=0.0032$) were predictive of non-relapse mortality (NRM). Levels of the 7 biomarkers at month 1 were not predictive of permanent cessation of immunosuppressive therapy for GVHD by 1 year post-transplant.

Conclusion: Levels of all 7 tested biomarkers at month 1 or month 2-3 post-transplant were prognostic for the occurrence of acute GVHD, chronic GVHD, and/or NRM in patients treated with PTCy as single-agent GVHD prophylaxis after MAC and HLA-matched-related or -unrelated alloBMT. Testing of these biomarkers at earlier post-transplant time periods or at patient-specific time points such as initiation of treatment for GVHD may have added clinical utility in the care of PTCy-treated patients.

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CD155 Regulates Regulatory T Cell Population and Attenuates Acute Graft-Versus-Host Disease

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The leukocyte adhesion molecule DNAM-1, also known as CD226, is constitutively expressed of most $CD4^+$ T cells, $CD8^+$ T cells and natural killer (NK) cells. The poliovirus receptor CD155, which is expressed on both hematopoietic and non-hematopoietic cells, is a ligand for DNAM-1 and TIGIT. Upon ligand binding, DNAM-1 mediates an activating signal in T cells and NK cells. TIGIT acts as a marker for regulatory T cell (Treg) subset and contributes to the Treg-mediated suppression. We have recently demonstrated a critical role of DNAM-1 on donor T cells in the development of acute GVHD in a mouse model (Nabekura, et al, PNAS, 2010, 2011). Recent reports also showed that DNAM-1 on donor cells promoted acute GVHD in a $CD4^+$ T cell-dependent manner via the inhibition of donor Treg expansion. Here, we found total body irradiation upregulated CD155 expression on recipient's dendritic cell. Therefore, we examined the role of CD155 expressed on host cells in the development of acute GVHD by using CD155-deficient mice.

Lethally irradiated CB6F1 wild type (WT) or *Cd155*$^{-/-}$ mice were transplanted with 5 x 10^6 bone marrow (BM) cells together with 2 x 10^6 splenic T cells derived from C57BL/6 mice. *Cd155*$^{-/-}$ recipient mice showed body weight loss significantly greater than did WT mice after transplantation ($P < 0.05$). Furthermore, *Cd155*$^{-/-}$ mice showed significantly shorter survival than WT mice ($P < 0.01$). Similar results were obtained in an acute GVHD model (C57BL/6 → BALB/c, $P < 0.05$). Further analyses revealed that *Cd155*$^{-/-}$ recipient mice showed decreased donor-derived Treg cell population, compared with WT recipient mice ($P < 0.01$). Depletion of Treg cells from transplanted splenic T cells resulted in comparable body weight loss and mortality between WT and *Cd155*$^{-/-}$ recipient mice after transplantation. These results suggest that host CD155 regulates the number of Treg cells and attenuated the development of acute GVHD.

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Impact of Acute and Chronic Graft-Versus-Host Disease on Outcomes after Single Cord Blood Transplantation: A Retrospective Analysis By the JSHCT Gvhd Working Group

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Background: Unrelated cord blood transplantation (UCBT) has increasingly been performed. Because cord blood units